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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 03/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,297	VAN URK ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2005 and 30 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-56,58-92 and 94-115* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-56,58-92 and 94-115* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/29/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 13 and December 30, 2004 has been entered.

2. Claims 54-56, 58-92 and 94-113 were previously pending. Applicants amended claims 54, 61, 76, 79, 82, 83, 86, 87, 90 and 111, and added new claims 114 and 115. Claims 54-56, 58-92 and 94-115 are pending and will be examined.

3. Applicants' amendments overcame the rejection of claims 82 and 84 under 35 U.S.C. 112, second paragraph. Other rejections are maintained for reasons given in the "Response to Arguments" section below.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on September 29, 2004 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Response to Arguments

5. Applicant's arguments filed September 13, 2004 have been fully considered but they are not persuasive.

Since the rejection for some of the claims were changed, Applicants' arguments regarding previously presented rejections are addressed with respect to the rejections presented in this office action.

A) Regarding the combination of references of Goody et al. and Fisher et al., which was present in all claim rejections, Applicants argue that since Fisher et al. teach only negative purification steps with respect to albumin, and teach that desorption from ion exchange materials is undesirable, therefore, Applicants conclude that Fisher requires that no desorption occurs (emphasis added). However, what Fisher et al. merely state (col. 1, line 68 to col. 2, line 3) is that such manipulation "increases the potential for adverse changes in the native character of the albumin molecules". Therefore, it does not mean that Fisher et al. require that albumin be purified with no desorption steps, and it does not mean that albumin purified using such steps will be adversely affected. Claims which were rejected over the combination of these two references were claims 54, 56, 59-67, 69, 70, 71, 74-76, 78, 79, 81, 90, 92, 95-102, 104-106, 109-111 and 113. Of these claims, the rejection is maintained for claims 54, 59, 60-62, 66, 67, 69, 70, 71, 90, 95-97, 101, 102 and 104-106.

B) Regarding the rejection of claims 55, 77, 80, 82, 84, 86, 88, 91 and 112 under 35 U.S.C. 103(a) over Goody et al. and Fisher et al. and in view of Shaklai et al., Applicants argue that Shaklai et al. has been applied for the teaching that glycosylated albumin peptides can bind to cation exchange resins, which provides no motivation to combine Goodey et al. and Fisher et al. The argument regarding combination of Goodey et al. and Fisher et al. has been addressed above. Further, Shaklai et al. teach purification of non-glycosylated albumin from glycosylated albumin in order to avoid complications when diabetic patients are treated with albumin. Therefore, Shaklai et al. provide a very strong motivation for removal of glycosylated albumin from albumin preparations.

The rejection is maintained, albeit in a different form, for claims 55, 77, 80, 91 and 112, and in the previously presented form for claims 82, 84, 86 and 88.

C) Regarding the rejection of claims 58 and 94 35 U.S.C. 103(a) over Goody et al. and Fisher et al. and in view of Curling, Applicants argue that since Curling does not provide a motivation for combining Goodey et al. with Fisher et al. The argument regarding combination of Goodey et al. and Fisher et al. has been addressed above.

The rejection is maintained.

D) Regarding the rejection of claims 68, 72, 73, 103, 107 and 108 under 35 U.S.C. 103(a) over Goody et al. and Fisher et al. and in view of Ohmura et al. and Chang, Applicants argue that Fisher et al. teaches away from chromatographic methods which require binding of albumin to the ion-exchange resin. This argument was addressed in part A). Applicants further argue that Chang teaches away from using positive chromatographic steps by teaching that a more efficient and economical method of purifying albumin by ion exchange is to bind contaminants to the resin. Therefore, Chang actually provides a strong motivation to use negative mode of ion exchange in the purification of albumin, supporting the motivation provided by Fisher et al.

The rejections are maintained.

E) Regarding the rejection of claims 83, 85, 87 and 89 under 35 U.S.C. 103(a) over Goody et al. and Fisher et al. and in view of Shaklai et al. and Chang, Applicants argue that Chang does not provide motivation for combining Goodey et al. and Fisher et al. This argument has been addressed above. Further, Applicants argue that the combination of Goodey et al., Fisher et al., Shaklai et al. and Chang does not provide positive AE steps. The positive AE steps are taught by Goodey et al.

The rejections are maintained.

Claim Interpretation

6. Before proceeding with art rejections meaning of some of the terms present in the claims, for which the definitions were not provided by Applicants, will be interpreted. "Chromatography in

the negative mode with respect to albumin" is interpreted to mean that albumin is not adsorbed onto the chromatographic matrix and is recovered in the flow-through, and "chromatography in the positive mode with respect to albumin" is interpreted to mean that albumin is adsorbed onto the chromatographic matrix. The term "initial albumin solution" is interpreted as the albumin solution before any of the purification steps. The term "glycoconjugate" is interpreted as any glycosylated material, such as glycoproteins, glycopeptides, etc.

7. A note regarding rejection of the claims in which the order of steps was reversed: reversal of steps is considered to be prima facie obvious (see MPEP 2144.04 IV C), therefore claims in which the only difference is reversal of steps will be rejected together, for example, claims 54-75 and 90-110, claims 76-78 and 79-81, claims (82, 84) and (86, 88), claims (83, 85 and 87, 89).

MPEP 2144.04 IV

C. Changes in Sequence of Adding Ingredients

Ex parte Rubin , 128 USPQ 440 (Bd. App. 1959) (Prior art reference disclosing a process of making a laminated sheet wherein a base sheet is first coated with a metallic film and thereafter impregnated with a thermosetting material was held to render prima facie obvious claims directed to a process of making a laminated sheet by reversing the order of the prior art process steps.). See also In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results); In re Gibson, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is prima facie obvious.).

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 54, 56, 61, 64, 65, 74-76, 78, 79, 81, 90, 92, 96, 99, 100, 109-11 and 113-115 are rejected under 35 U.S.C. 102(b) as being anticipated by Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS and in the previous office action), supported by Ohmura et al. (EP 0 570 916 A2; cited in the IDS and in the previous office action).

Regarding claims 54, 76, 79, 90 and 111, Fisher et al. teach a process for albumin purification (Abstract), the process comprising:

(1) subjecting the albumin solution to cation exchange (CE) chromatography in the negative mode with respect to albumin in order to yield an albumin-containing CE product (Fisher et al. teach contacting the albumin solution to be purified with a CE exchange matrix to remove proteins having isoelectric points below that of albumin, to yield an albumin-containing flow-through (col. 2, lines 23-30; col. 3, lines 57-63; col. 4, lines 1-7).);

(2) subjecting the albumin-containing CE product, with or without intervening purification step, to anion exchange (AE) chromatography to yield an albumin-containing AE product (Fisher et al. teach contacting the albumin solution to be purified with an AE exchange matrix to remove proteins having isoelectric points above that of albumin (col. 2, lines 23-30; col. 3, lines 46-56; col. 4, lines 1-7).);

(3) placing the albumin-containing AE product, without further purification, into a final container for therapeutic use (Fisher et al. teach concentrating and lyophilization of the final product to form a theraputic solution (col. 3, lines 64-68; col. 5, lines 10-22; col. 11, lines 7-10). Fisher et al. do not specifically teach placing the solution in a container, but since it was lyophilized, for example, it had to be placed into a suitable container, therefore Fisher et al. inherently teach a container.)

Regarding claims 74 and 76, Fisher et al. teach subjecting the anion-exchange product to

pH-adjustment (col. 3, lines 57-59).

Regarding claim 79 and 111, Fisher et al. teach subjecting the cation-exchange product to pH-adjustment (col. 2, lines 30-32).

Regarding claims 79, 90 and 111, Fisher et al. specifically teach that the order of chromatographic steps is not important (col. 2, lines 38-40).

Regarding claims 56 and 92, Fisher et al. teach CE step utilizing a matrix such as SP-Sepadex (col. 2, line 66). Fisher et al. do not specifically teach sulfopropyl subsituents as cation exchangers. As evidenced by Ohmura et al., SP stands for a sulfopropyl group, for example, SP-Sephadex is sulfopropyl-dextran (page 5, lines 37-40). Since Fisher et al. teach SP-Sepadex, they inherently teach sulfoprpyl groups as cation exchangers.

Regarding claims 61, 78, 81, 96, 109 and 113, Fisher et al. teach adjusting the pH of the albumin solution to between 5.1 and 5.5 before loading onto CE column (col. 3, lines 57-65; col. 4, lines 19-22).

Regarding claims 64 and 99, Fisher et al. teach AE step run in a negative mode with respect to albumin (col. 2, lines 30-38; col. 3, lines 46-56; col. 4, lines 1-7).

Regarding claims 65 and 100, Fisher et al. teach that albumin solution, which undergoes CE chromatography has a pH of 5.1-5.5 (col. 2, line 32).

Regarding claims 75 and 110, Fisher et al. teach primary separation of albumin from other cell components (col. 2, lines 18-23; col. 3, lines 45).

Regarding claims 114 and 115, Fisher et al. teach albumin solution of pH of about 4.5 to 4.9 loaded onto CE column (col. 2, lines 25, 26), therefore Fisher et al. teach pH within the range of 4.5-6.0.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejections based on the Fisher et al. reference

11. Claims 55, 77, 80, 91 and 112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS and in the previous office action) and Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984; cited in the previous office action).

A) Claim 55 is drawn to a process according to claim 54 wherein the initial albumin solution contains glycosylated albumin and the glycosylated albumin is bound during the cation exchange step. Claim 77 is drawn to a process according to claim 76 wherein the initial albumin solution contains glycosylated albumin and the glycosylated albumin is bound during the cation exchange step. Claim 80 is drawn to a process according to claim 79 wherein the initial albumin solution contains glycosylated albumin and the glycosylated albumin is bound during the cation exchange step. Claim 91 is drawn to a process according to claim 90 wherein the initial albumin solution contains glycosylated albumin and the glycosylated albumin is bound during the cation exchange step. Claim 112 is drawn to a process according to claim 111 wherein the initial albumin solution contains glycosylated albumin and the glycosylated albumin is bound during the cation exchange step.

B) Fisher et al. do not teach initial albumin solution containing glycosylated albumin and the glycosylated albumin being bound during the cation exchange step.

C) Regarding claims 55, 77, 80, 91 and 112, Shaklai et al. teach that 10% of albumin present in human plasma is glycosylated (Abstract). Glycosylated albumin has altered ligand binding properties: bilirubin binding is lower by 50% and fatty-acid binding is reduced 20-fold (Abstract; Fig. 4, Fig. 5, page 3814, the last paragraph; page 3815). Shaklai et al. teach separation of glycosylated albumin (= glycoconjugate) from non-glycosylated albumin on a GlycoGel B affinity column, to which glycosylated albumin bound, and non-glycosylated albumin was collected in a flow through (page 3812, seventh paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have removed glycosylated albumin by affinity chromatography of Shaklai et al. in the method of albumin purification by Fisher et al. The motivation to do so, provided by Shaklai et al., would have been that glycosylated albumin had impaired function of binding and transporting of fatty acids (Abstract; page 3816, the last paragraph) and that albumin glycosylation may contribute to long term diabetic complications (page 3812, second paragraph). Therefore, removing glycosylated albumin from albumin solution according to Shaklai et al. enhances the ability of Fisher et al. to obtain highly purified albumin for therapeutic treatments (col. 8, lines 7-10), without a danger of introducing into a patient an inactive protein which might also contribute to diabetic complications.

12. Claims 59-62, 95-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS and in the previous office action) and Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action).

A) Fisher et al. do not teach conditioning of albumin solution with octanoate salt prior to cation exchange step.

B) Regarding claims 59-62, 95-97, Goodey et al. teach addition of sodium octanoate to a final concentration of 1-10 mM (page 16, lines 5-13).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have added sodium octanoate of Goodey et al. to albumin solution of Fisher et al. The motivation to do so, provided by Goodey et al., would have been that sodium octanoate protects albumin from polymerization (page 16, lines 7, 8).

Rejections based on Goodey et al. and Fisher et al.

13. Claims 54, 59-63, 66, 67, 69-71, 90, 95-98, 101, 102 and 104-106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action) and of Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS and in the previous office action), supported by Ohmura et al. (EP 0 570 916 A2; cited in the IDS and in the previous office action).

A) Regarding claims 54 and 90, Goodey et al. teach a process for purifying an albumin solution, the process comprising:

(1) subjecting the albumin solution to cation exchange (CE) chromatography in the positive mode with respect to albumin in order to yield an albumin-containing CE product (Goodey et al. teach CE chromatography of an albumin solution on cation exchanger; see page 1, lines 26-31; page 2, lines1-10);

(2) subjecting the albumin-containing CE product, with or without intervening purification step, to anion exchange (AE) chromatography to yield an albumin-containing AE product (Goodey et al. teach a process comprising CE and AE chromatography, with a possible steps of affinity chromatography (AC), ultrafiltration and gel permeation chromatography before AE chromatography; see page 2, lines 6-31; page 3, lines 1-16);

(3) placing the albumin-containing AE product, without further purification, into a final container for therapeutic use (Goodey et al. teach placing the purified albumin into a plurality of vials (page 6, lines 28-30) and placing the albumin solution into a bulk product formulation vessel, followed by completing formulation by addition of pharmacetutically acceptable excipients (page 27, lines 20-22).)

Regarding claims 59, 60 and 95, Goodey et al. teach initial albumin solution with octanoate concentration of 1-10 mM (page 3, lines 20-22; page 16, lines 9-11).

Regarding claims 61, 62, 96 and 97, Goodey et al. teach adjusting the pH of albumin solution and conditioning of albumin solution by addition of octanoate salt prior to cation exchange step (page 3, lines 20-22; page 16, lines 9-11).

Regarding claims 63 and 98, Goodey et al. teach AE step utilizing a matrix such as DEAE-Spherodex, Q-Hyper D, DEAE-cellulose, QAE-cellulose, TMAE, DMAE, DEAE Fractogel or DEAE Sepharose FF (page 25, lines 12-14). Goodey et al. do not specifically teach dialkylaminoalkyl subsituents as anion exchangers. As evidenced by Ohmura et al., DEAE means diethylaminoethyl group (page 6, lines 11-15), which is a species of dialkylaminoalkyl groups (Lindquist et al., col. 3, lines 53-56). Therefore, since Goodey et al. teach DEAE-Spherodex, DEAE Fractogel or DEAE Sepharose FF, they teach dialkylaminoalkyl subsituents as anion exchangers.

Regarding claims 66 and 101, Goodey et al. teach that solution undergoing anion exchange chromatography has a conductivity of less than 4 mS/cm, namely, 2.5 ± 0.5 mS/cm (page 32, lines 1, 2).

Regarding claims 67 and 102, Goodey et al. teach AE step run in a positive mode with respect to albumin (page 25, lines 9-29).

Regarding claims 69 and 104, Goodey et al. teach ultrafiltration of albumin solution to a concentration between 20-120 g/L or 80-110 g/L before loading onto AE column (page 24, lines 20-24).

Regarding claims 70 and 105, Goodey et al. teach AE column equilibrated with a buffer with conductivity in the range of 1-4 mS/cm or 1.5-5 mS/cm (page 25, line 20; page 32, line 1).

Regarding claims 71 and 106, Goodey et al. teach elution of albumin from CE column with a solution of octanoate (page 31, lines 21-25), which has specific activity for albumin (page 2, lines 1-4). Goodey et al. do not teach elution of albumin from AE column using a solution of octanoate. However, they teach that pH of the eluting solution should be about 5.5, so that the binding of octanoate causes a significant overall charge difference (page 31, lines 23, 24). They also teach loading the eluate from the cation exchanger onto AE column equilibrated with a buffer of pH 5.5 (page 31, lines 27-29).

B) Goodey et al. do not teach albumin purification using CE or AE chromatography run in a negative mode with respect to albumin.

C) Fisher et al. teach albumin purification using CE and AE chromatography in a negative mode with respect to albumin (Abstract; col. 2, lines 12-16).

Regarding claims 54 and 90, Fisher et al. teach subjecting the albumin solution to cation exchange (CE) chromatography in the negative mode with respect to albumin in order to yield an albumin-containing CE product (Fisher et al. teach contacting the albumin solution to be purified with a CE exchange matrix to remove proteins having isoelectric points below that of albumin (col. 2, lines 23-30; col. 3, lines 57-63; col. 4, lines 1-7). Fisher et al. teach adjusting the pH of the albumin solution to between 5.1 and 5.5 before loading onto CE column (col. 3, lines 57-65; col. 4, lines 19-22).

It would have been *prima facie* obvious to one of ordinary skill in the art to add the CE and AE chromatography steps run in a negative mode with respect to albumin of Fisher et al. to the albumin purification method of Goodey et al. The motivation to do so, provided by Fisher et al., would have been that using ion exchange in negative mode with respect to albumin maintained albumin in solution, and resulted in efficient albumin purification while minimizing potential alterations to albumin structure (col. 2, lines 4-17). The teaching of Fisher et al. regarding the anion exchange purification therefore enhances the ability of Goodey et al. to obtain highly purified albumin therapeutic treatments (Goodey et al., page 1, lines 1-25).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have eluted albumin from AE column with a buffer containing a compound having a specific affinity for albumin. The motivation to do so would have been that albumin elution could be accomplished with more specificity and efficiency, since no other proteins bound to a compound with specific affinity for albumin.

14. Claims 82, 84, 86 and 88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action) and Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS and in the previous office action), and further in view Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984; cited in the previous office action).

A) Regarding claims 82 and 86, Goodey et al. teaches a process for purifying an albumin solution, the process comprising the steps of:

(i) subjecting an albumin solution to a CE chromatography step run in positive mode with respect to albumin (Goodey et al. teach CE chromatography of an albumin solution on cation exchanger; see page 1, lines 26-31; page 2, lines 1-10; page 21, lines 1-26);

(ii) collecting an albumin-containing CE eluate (Goodey et al. teach collecting 6.5 volumes

of eluate; page 21, lines 26-28);

(iii) subjecting the CE eluate to an AE chromatography step run in a positive mode with respect to the albumin (Goodey et al. teach AE chromatography run in a positive mode with respect to albumin; page 25, lines 9-26);

(iv) collecting an albumin-containing AE eluate (Goodey et al. teach collecting albumin-containing eluate; page 3, lines 4-16; page 25, lines 27-29);

(v) subjecting the AE eluate to an affinity chromatography (AC) step run in positive mode with respect to the albumin (Goodey et al. teach AC chromatography of albumin on a column containing a matrix which specifically binds albumin, such as DBA (Delta Blue Agarose) matrix; page 22; page 23, lines 1-20);

(vi) collecting the albumin-containing AC eluate (Goodey et al. teach collecting the AC eluate; page 3, lines 4-16; page 23, lines 16-20).

Regarding claims 84 and 88, Goodey et al. teach adjusting the pH of albumin solution and conditioning of albumin solution by addition of octanoate salt prior to cation exchange step (page 3, lines 20-22; page 16, lines 9-11).

E) Goodey et al. do not teach albumin purification using CE or AE chromatography run in a negative mode with respect to albumin.

F) Fisher et al. teach albumin purification using CE and AE chromatography in a negative mode with respect to albumin (Abstract; col. 2, lines 12-16). Fisher et al. teach that the order of ion exchange steps is not critical (col. 2, lines 38-40).

Regarding claims 82 and 86, Fisher et al. teach a process for albumin purification (Abstract), the process comprising:

(ix) subjecting the albumin solution to CE chromatography in the negative mode with

respect to albumin (Fisher et al. teach contacting the albumin solution to be purified with a CE exchange matrix to remove proteins having isoelectric points below that of albumin (col. 2, lines 23-30; col. 3, lines 57-63; col. 4, lines 1-7); Fisher et al. teach adjusting the pH of the albumin solution to between 5.1 and 5.5 before loading onto CE column (col. 3, lines 57-65; col. 4, lines 19-22).

(x) collecting the albumin-containing CE flow through (Fisher et al. teach collecting the fluid containing albumin after CE chromatography; col. 3, lines 64-66);

(xi) subjecting the albumin solution to AE chromatography in the negative mode with respect to albumin (Fisher et al. teach contacting the albumin solution to be purified with an AE exchange matrix to remove proteins having isoelectric points above that of albumin (col. 2, lines 23-30; col. 3, lines 46-56; col. 4, lines 1-7);

(xii) collecting the albumin-containing AE flow through (Fisher et al. teach collecting the fluid containing albumin after AE chromatography; col. 3, lines 54-56).

G) Neither Goodey et al. nor Fisher et al. teach affinity chromatography run in a negative mode with respect to albumin and in positive mode with respect to glyconjugates.

H) Regarding claims 82 and 86, Shaklai et al. teach that 10% of albumin present in human plasma is glycosylated (Abstract). Glycosylated albumin has altered ligand binding properties: bilirubin binding is lower by 50% andfatty-acid binding is reduced 20-fold (Abstract; Fig. 4, Fig. 5, page 3814, the last paragraph; page 3815). Shaklai et al. teach separation of glycosylated albumin (= glycoconjugate) from non-glycosylated albumin on a GlycoGel B affinity column, to which glycosylated albumin bound, and non-glycosylated albumin was collected in a flow through (page 3812, seventh paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art to add the CE and

AE chromatography steps run in a negative mode with respect to albumin of Fisher et al. to the albumin purification method of Goodey et al. The motivation to do so, provided by Fisher et al., would have been that using ion exchange in negative mode with respect to albumin maintained albumin in solution, and resulted in efficient albumin purification while minimizing potential alterations to albumin structure (col. 2, lines 4-17).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have removed glycosylated albumin by affinity chromatography of Shaklai et al. in the method of albumin purification by Goodey et al. and Fisher et al. The motivation to do so, provided by Shaklai et al., would have been that glycosylated albumin had impaired function of binding and transporting of fatty acids (Abstract; page 3816, the last paragraph) and that albumin glycosylation may contribute to long term diabetic complications (page 3812, second paragraph). Therefore, removing glycosylated albumin from albumin solution according to Shaklai et al. enhances the ability of Goodey et al. and Fisher et al. to obtain highly purified albumin for therapeutic treatments (Goodey et al., page 1, lines 1-25), without a danger of introducing into a patient an inactive protein which might also contribute to diabetic complications.

15. Claims 58 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action) in view of Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS and in the previous office action) as applied to claims 54 and 90 above, and further in view of Curling ("Methods of Plasma Protein Fractionation", pp. 77-91, 1980; cited in the IDS and in the previous office action).

A) Claim 58 is drawn to the method of claim 54 wherein the initial albumin solution has an albumin concentration of 10-250 g/L, and claim 94 is drawn to the method of claim 90 wherein the initial albumin solution has an albumin concentration of 10-250 g/L.

B) Neither Goodey et al. nor Fisher et al. teach initial albumin solution has an albumin concentration of 10-250 g/L. Goodey et al. teach obtaining albumin from large-scale fermentation, with a fermenter the size of 4000 L (page 13, lines 20-23). They also teach that the expected yield of albumin is greater than 1.5 g/L of culture. Therefore, the total amount of albumin obtained from 4000 L would be at least 6000 g of albumin. They also teach that after pretreatment and centrifugation 75% of the albumin present id diluted culture is recovered, which would translate into at least 4500 g of albumin in a solution of unspecified volume, to be loaded onto an ion exchange column.

C) Curling teaches industrial scale purification of albumin on AE and CE columns, with 500 g of albumin in 16 L (about 31 g/L albumin) loaded onto the columns (Fig. 2, page 81, paragraphs 3-6; Table 1).

It would have been prima facie obvious to one of ordinary skill in the art to have used initial albumin concentrations of Curling (greater than 10 g/L) in the combined method of Goodey et al. and Fisher et al. The motivation to do so, provided by Curling, would have been that purification with this albumin concentration resulted in a 97% pure product (page 82, second paragraph).

16. Claims 68, 72, 73, 103, 107 and 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action) in view of Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS and in the previous office action) as applied to claims 54, 67, 71, 90, 102 and 106 above, and further in view of Ohmura et al. (EP 0 570 916 A2; cited in the IDS and in the previous office action) and Chang (EP 0 422 769 A1; cited in the IDS and in the previous office action).

A) Claim 68 is drawn to a process according to claim 67 wherein the albumin solution which undergoes positive mode anion exchange chromatography has a pH of 6.0-8.0, and claim 73

is drawn to the process according to claim 67 wherein the albumin is eluted in the anion exchange step with a buffer of pH 6.0-8.0. Claim 103 is drawn to a process according to claim 102 wherein the albumin solution which undergoes positive mode anion exchange chromatography has a pH of 6.0-8.0, and claim 108 is drawn to the process according to claim 102 wherein the albumin is eluted in the anion exchange step with a buffer of pH 6.0-8.0. Claim 72 is drawn to a process of claim 71 wherein the buffer comprises 20-90 mM phosphoric acid salt, and claim 107 is drawn to a process of claim 106 wherein the buffer comprises 20-90 mM phosphoric acid salt.

B) Neither Goodey et al. nor Fisher et al. teach albumin solution which undergoes positive mode anion exchange chromatography with a pH of 6.0-8.0, or the albumin being eluted in the anion exchange step with a buffer of pH 6.0-8.0. Goodey et al. do not teach albumin elution buffer comprising 20-90 mM phosphoric acid salt. Fisher et al. teach a suitable eluent for a material absorbed on AE column being 0.1 M sodium phosphate (col. 4, lines 28-30).

C) Ohmura et al. teach purification of albumin comprising AE chromatography step run in a positive mode with respect to albumin (page 6, lines 21-24). They teach that albumin can be adsorbed onto AE column using a phosphate buffer of pH 6 to 8 and salt concentration of 0.001-0.05 M, and eluted from the column using buffer with the same pH range and salt concentration of 0.05 to 1 M (page 6, lines 18-24). They teach anion exchange column buffer of 50 mM phosphate (page 11, lines 49-51). Chang teaches albumin purification comprising a step of AE chromatography (Abstract). Chang teaches that at pH > 6.1 albumin becomes more readily bound to the anion exchange column (page 4, lines 31-33).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used a buffer with a pH of 6.0-8.0 of Ohmura et al. in the combined albumin purification method of Goodey et al. and Fisher et al. The motivation to do so, provided by Chang,

would have been that at pH > 6.1 albumin bound better to AE column than contaminating proteins (page 4, lines 31-33).

17. Claims 83, 85, 87 and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS and in the previous office action) and Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS and in the previous office action), in view of Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984; cited in the previous office action), and further in view of Chang (EP 0 422 769 A1; cited in the IDS and in the previous office action).

A) Regarding claims 83 and 87, Goodey et al. teaches a process for purifying an albumin solution, the process comprising the steps of:

(i) subjecting an albumin solution to a CE chromatography step run in positive mode with respect to albumin (Goodey et al. teach CE chromatography of an albumin solution on cation exchanger; see page 1, lines 26-31; page 2, lines 1-10; page 21, lines 1-26);

(ii) collecting an albumin-containing CE eluate (Goodey et al. teach collecting 6.5 volumes of eluate; page 21, lines 26-28);

(iii) subjecting the CE eluate to an AE chromatography step run in a positive mode with respect to the albumin (Goodey et al. teach AE chromatography run in a positive mode with respect to albumin; page 25, lines 9-26);

(iv) collecting an albumin-containing AE eluate (Goodey et al. teach collecting albumin-containing eluate; page 3, lines 4-16; page 25, lines 27-29);

(v) subjecting the AE eluate to an affinity chromatography (AC) step run in positive mode with respect to the albumin (Goodey et al. teach AC chromatography of albumin on a column containing a matrix which specifically binds albumin, such as DBA (Delta Blue Agarose) matrix; page 22; page 23, lines 1-20);

(vi) collecting the albumin-containing AC eluate (Goodey et al. teach collecting the AC eluate; page 3, lines 4-16; page 23, lines 16-20).

Regarding steps (xi) and (xii) of claim 83 (or steps (ix) and (x) of claim 87), these are repeated steps (iii) and (iv). Goodey et al. do not specifically teach repeating AE step in a positive mode with respect to albumin.

Regarding claims 85 and 89, Goodey et al. teach adjusting the pH of albumin solution and conditioning of albumin solution by addition of octanoate salt prior to cation exchange step (page 3, lines 20-22; page 16, lines 9-11).

B) Goodey et al. do not teach albumin purification using CE chromatography run in a negative mode with respect to albumin.

C) Fisher et al. teach albumin purification using CE chromatography in a negative mode with respect to albumin (Abstract; col. 2, lines 12-16). Fisher et al. teach that the order of ion exchange steps is not critical (col. 2, lines 38-40).

Regarding claims 83 and 87, Fisher et al. teach a process for albumin purification (Abstract), the process comprising:

(ix) subjecting the albumin solution to CE chromatography in the negative mode with respect to albumin (Fisher et al. teach contacting the albumin solution to be purified with a CE exchange matrix to remove proteins having isoelectric points below that of albumin (col. 2, lines 23-30; col. 3, lines 57-63; col. 4, lines 1-7. Fisher et al. teach adjusting the pH of the albumin solution to between 5.1 and 5.5 before loading onto CE column (col. 3, lines 57-65; col. 4, lines 19-22).);

(x) collecting the albumin-containing CE flow through (Fisher et al. teach collecting the fluid containing albumin after CE chromatography; col. 3, lines 64-66);

D) Neither Goodey et al. nor Fisher et al. teach repeating AE chromoatography steps or affinity chromatography run in a negative mode with respect to albumin and in positive mode with respect to glyconjugates .

E) Regarding claims 83 and 87, Chang teaches repeating AE chromatography steps to remove contaminating proteins from albumin solution (Abstract; page 4, lines 17-39).

F) Shaklai et al. teach that 10% of albumin present in human plasma is glycosylated (Abstract). Glycosylated albumin has altered ligand binding properties: bilirubin binding is lower by 50% andfatty-acid binding is reduced 20-fold (Abstract; Fig. 4, Fig. 5, page 3814, the last paragraph; page 3815). Shaklai et al. teach separation of glycosylated albumin (= glycoconjugate) from non-glycosylated albumin on a GlycoGel B affinity column, to which glycosylated albumin bound, and non-glycosylated albumin was collected in a flow through (page 3812, seventh paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art to add the CE chromatography step run in a negative mode with respect to albumin of Fisher et al. to the albumin purification method of Goodey et al. The motivation to do so, provided by Fisher et al., would have been that using ion exchange in negative mode with respect to albumin maintained albumin in solution, and resulted in efficient albumin purification while minimizing potential alterations to albumin structure (col. 2, lines 4-17).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have removed glycosylated albumin by affinity chromatography of Shaklai et al. in the method of albumin purification by Goodey et al. and Fisher et al. The motivation to do so, provided by Shaklai et al., would have been that glycosylated albumin had impaired function of binding and transporting of fatty acids (Abstract; page 3816, the last paragraph) and that albumin glycosylation

may contribute to long term diabetic complications (page 3812, second paragraph). Therefore, removing glycosylated albumin from albumin solution according to Shaklai et al. enhances the ability of Goodey et al. and Fisher et al. to obtain highly purified albumin for therapeutic treatments (Goodey et al., page 1, lines 1-25), without a danger of introducing into a patient an inactive protein which might also contribute to diabetic complications.

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have repeated the AE steps in the albumin purification method of Goodey et al., Fisher et al. and Shaklai et al. according to Chang. The motivation to do so, provided by Chang, would have been that repeating AE steps resulted in albumin purity of greater than 99% (page 4, lines 44-46).

18. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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